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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C F R § 1 53(b))

Attorney Docket No.	NMEDP001-2
First Inventor or Application Identifier	Snutch, Terry P.
Title	Novel Human Calcium Channels and...
Express Mail Label No.	EL362857074US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents

ADDRESS TO: Box Patent Application
Washington, DC 20231

1. [✓] * Fee Transmittal Form *(e.g., PTO/SB/17)*
(Submit an original and a duplicate for fee processing)

2. [✓] Specification [Total Pages 31]
(preferred arrangement set forth below)
- Descriptive title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings *(if filed)*
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

3. [✓] Drawing(s) *(35 U.S.C. 113)* [Total Sheets 4]

4. Oath or Declaration [Total Pages 3]
a. [✓] Newly executed (original or copy)
b. [ ] Copy from a prior application (37 C.F.R. § 1.63(d))
(for continuation/divisional with Box 16 completed)
i. [ ] DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

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5. [ ] Microfiche Computer Program *(Appendix)*

6. Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
a. [✓] Computer Readable Copy
b. [✓] Paper Copy (identical to computer copy)
c. [✓] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. [ ] Assignment Papers (cover sheet & document(s))
8. [ ] 37 C.F.R.§3.73(b) Statement *(when there is an assignee)* [✓] Power of Attorney
9. [ ] English Translation Document *(if applicable)*
10. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
11. [ ] Preliminary Amendment
12. [✓] Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
13. [✓] * Small Entity Statement(s) *(PTO/SB/09-12)* [ ] Statement filed in prior application, Status still proper and desired
14. [ ] Certified Copy of Priority Document(s)
(if foreign priority is claimed)
15. [ ] Other: .....

16. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment.*
[ ] Continuation [ ] Divisional [✓] Continuation-in-part (CIP) of prior application No. 09 / 030,482
Prior application information. Examiner Basi, N. Group / Art Unit 1646

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

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City		State		Zip Code	
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Name (Print/Type)	Marina T. Larson, Ph.D.	Registration No. (Attorney/Agent)	32,038
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Oppedahl & Larson

Applicant or Patentee: SNUTCH ET AL Attorney's Docket No. NMED.P-001-2
Serial or Patent No.: TBA Filed or Issued: HEREWITH
For: NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am
( ) the owner of the small business concern identified below:
(X) an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN NeuroMed Technologies Inc.
ADDRESS OF CONCERN ~~3963 W. 24th Avenue~~ 400-601 West Broadway, Vancouver, Canada ~~V6S 1M1~~ V5Z 4C2

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the above-captioned invention which is described in

(X) the specification filed herewith
( ) Application Serial No. _____, filed _____.
( ) Patent No. _____, issued _____.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e). *Note: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME _____
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( ) INDIVIDUAL ( ) SMALL BUSINESS CONCERN ( ) NONPROFIT ORGANIZATION

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I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Natalie Dakers TITLE Chief Operating Officer
ADDRESS OF PERSON SIGNING 400 - 601 West Broadway
Vancouver, BC V5Z 4C2
SIGNATURE _____ DATE 99/07/02

NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

This application is a continuation-in-part of copending US Patent Application No. Serial No. 09/030,482, filed February 25, 1998, which is a 111(a) application claiming priority from US Provisional Application No. 60/039,204, filed February 28, 1997, both of which are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to novel mammalian (including human) calcium channel compositions, and to the expression of these compositions in cell lines for use in evaluating calcium channel function and the behavior of compositions which modulate calcium channel function.

BACKGROUND OF THE INVENTION

The rapid entry of calcium into cells is mediated by a class of proteins called voltage-gated calcium channels. Calcium channels are a heterogeneous class of molecules that respond to depolarization by opening a calcium-selective pore through the plasma membrane. The entry of calcium into cells mediates a wide variety of cellular and physiological responses including excitation-contraction coupling, hormone secretion and gene expression. In neurons, calcium entry directly affects membrane potential and contributes to electrical properties such as excitability, repetitive firing patterns and pacemaker activity. Miller, R.J. (1987) "Multiple calcium channels and neuronal function." *Science* 235:46-52. Calcium entry further affects neuronal functions by directly regulating calcium-dependent ion channels and modulating the activity of calcium-dependent enzymes such as protein kinase C and calmodulin-dependent protein kinase II. An increase in calcium concentration at the presynaptic nerve terminal triggers the release of neurotransmitter. Calcium entry also plays a

role in neurite outgrowth and growth cone migration in developing neurons and has been implicated in long-term changes in neuronal activity.

In addition to the variety of normal physiological functions mediated by calcium channels, they are also implicated in a number of human disorders. Recently, mutations identified in human and mouse calcium channel genes have been found to account for several disorders including, familial hemiplegic migraine, episodic ataxia type 2, cerebellar ataxia, absence epilepsy and seizures. Fletcher, et al. (1996) "Absence epilepsy in tottering mutant mice is associated with calcium channel defects." *Cell* 87:607-617; Burgess, et al. (1997) "Mutation of the Ca2+ channel β subunit gene Cchb4 is associated with ataxia and seizures in the lethargic (lh) mouse." *Cell* 88:385-392; Ophoff, et al. (1996) "Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4." *Cell* 87:543-552; Zhuchenko, O. et al. (1997) "Autosomal dominant cerebellar ataxia (SCA6) associated with the small polyglutamine expansions in the α1A-voltage-dependent calcium channel." *Nature Genetics* 15:62-69.

The clinical treatment of some disorders has been aided by the development of therapeutic calcium channel antagonists. Janis, et al. (1991) in *Calcium Channels: Their Properties, Functions, Regulation and Clinical Relevance.* CRC Press, London.

Native calcium channels have been classified by their electrophysiological and pharmacological properties as T, L, N, P and Q types (for reviews see McCleskey, et al. (1991) "Functional properties of voltage-dependent calcium channels." *Curr. Topics Membr.* 39: 295-326, and Dunlap, et al. (1995) "Exocytotic Ca^{2+} channels in mammalian central neurons." *Trends Neurosci.* 18:89-98.). T-type (or low voltage-activated) channels describe a broad class of molecules that activate at negative potentials and are highly sensitive to changes in resting potential. The L, N, P and Q-type channels activate at more positive potentials and display diverse kinetics and voltage-dependent properties. There is some overlap in biophysical properties of the high voltage-activated channels, consequently pharmacological profiles are useful to further distinguish them. L-type channels are sensitive

to dihydropyridine (DHP) agonists and antagonists, N-type channels are blocked by the *Conus geographus* peptide toxin, ω-conotoxin GVIA, and P-type channels are blocked by the peptide ω-agatoxin IVA from the venom of the funnel web spider, *Agelenopsis aperta*. A fourth type of high voltage-activated Ca channel (Q-type) has been described, although whether the Q- and P-type channels are distinct molecular entities is controversial (Sather et al. (1993) "Distinctive biophysical and pharmacological properties of class A (B1) calcium channel α1 subunits." *Neuron* 11: 291-303; Stea, et al. (1994) "Localization and functional properties of a rat brain α1A calcium channel reflect similarities to neuronal Q- and P-type channels." *Proc Natl Acad Sci (USA)* 91: 10576-10580.). Several types of calcium conductances do not fall neatly into any of the above categories and there is variability of properties even within a category suggesting that additional calcium channels subtypes remain to be classified.

Biochemical analyses show that neuronal high-threshold calcium channels are heterooligomeric complexes consisting of three distinct subunits (α_1, $\alpha_2\delta$ and β)(reviewed by De Waard, et al. (1997) in *Ion Channels*, Volume 4, edited by Narahashi, T. Plenum Press, New York). The α_1 subunit is the major pore-forming subunit and contains the voltage sensor and binding sites for calcium channel antagonists. The mainly extracellular α_2 is disulphide-linked to the transmembrane δ subunit and both are derived from the same gene and are proteolytically cleaved *in vivo*. The β subunit is a non-glycosylated, hydrophilic protein with a high affinity of binding to a cytoplasmic region of the α_1 subunit. A fourth subunit, γ, is unique to L-type Ca channels expressed in skeletal muscle T-tubules. The isolation and characterization of γ-subunit-encoding cDNAs is described in US Patent No. 5,386,025 which is incorporated herein by reference.

Molecular cloning has revealed the cDNA and corresponding amino acid sequences of six different types of α_1 subunits (α_{1A}, α_{1B}, α_{1C}, α_{1D}, α_{1E} and α_{1S}) and four types of β subunits (β_1, β_2, β_3 and β_4)(reviewed in Stea, A., Soong, T.W. and Snutch, T.P. (1994) "Voltage-gated calcium channels." in *Handbook of Receptors and Channels*. Edited by R.A. North, CRC

Press.). PCT Patent Publication WO 95/04144, which is incorporated herein by reference, discloses the sequence and expression of α_{1E} calcium channel subunits.

The different classes of $\alpha 1$ and β subunits have been identified in different animals including, rat, rabbit and human and share a significant degree of amino acid conservation across species (for examples see: Castellano, et al. (1993) "Cloning and expression of a third calcium channel β subunit." *J. Biol. Chem.* 268: 3450-3455; Castellano, et al. (1993) "Cloning and expression of a neuronal calcium channel β subunit." *J. Biol. Chem.* 268: 12359-12366; Dubel, et al. (1992). "Molecular cloning of the α_1 subunit of an ω-conotoxin-sensitive calcium channel." *Proc. Natl. Acad. Sci. (USA)* 89: 5058-5062; Fujita, et al.. (1993) "Primary structure and functional expression of the ω-conotoxin-sensitive N-type calcium channel from rabbit brain." *Neuron* 10: 585-598; Mikami, et al.. (1989). "Primary structure and functional expression of the cardiac dihydropyridine-sensitive calcium channel." *Nature* 340: 230-233; Mori, et al. (1991) "Primary structure and functional expression from complementary DNA of a brain calcium channel." *Nature* 350: 398-402; Perez-Reyes, et al. (1992). "Cloning and expression of a cardiac/brain ß subunit of the L-type calcium channel." *J. Biol. Chem.* 267: 1792-1797; Pragnell, et al. (1991). "Cloning and tissue-specific expression of the brain calcium channel β-subunit." *FEBS Lett.* 291: 253-258; Snutch, et al. (1991) "Distinct calcium channels are generated by alternative splicing and are differentially expressed in the mammalian CNS." *Neuron* 7: 45-57; Soong, et al. (1993) "Structure and functional expression of a member of the low voltage-activated calcium channel family." *Science* 260: 1133-1136; Tomlinson, et al. (1993) "Functional properties of a neuronal class C L-type channel." *Neuropharmacology* 32: 1117-1126; Williams, et al. (1992) "Structure and functional expression of $\alpha 1$, $\alpha 2$, and ß subunits of a novel human neuronal calcium channel subtype." *Neuron* 8: 71-84; Williams, et al. (1992) "Structure and functional expression of an ω-conotoxin-sensitive human N-type calcium channel." *Science* 257: 389-395.

In some expression systems the α_1 subunits alone can form functional calcium channels although their electrophysiological and pharmacological properties can be differentially modulated by coexpression with any of the four β subunits. Until recently, the reported modulatory affects of β subunit coexpression were to mainly alter kinetic and voltage-dependent properties. More recently it has been shown that β subunits also play crucial roles in modulating channel activity by protein kinase A, protein kinase C and direct G-protein interaction. (Bourinet, et al. (1994) "Voltage-dependent facilitation of a neuronal α1C L-type calcium channel." *EMBO J.* 13: 5032-5039; Stea, et al. (1995) "Determinants of PKC-dependent modulation of a family of neuronal calcium channels." *Neuron* 15:929-940; Bourinet, et al. (1996) "Determinants of the G-protein-dependent opioid modulation of neuronal calcium channels." *Proc. Natl. Acad. Sci. (USA)* 93: 1486-1491.)

The electrophysiological and pharmacological properties of the calcium channels cloned to date can be summarized as shown in Table 1. While the cloned α_1 subunits identified to date correspond to several of the calcium channels found in cells, they do not account for all types of calcium conductances described in native cells. For example, they do not account for the various properties described for the heterogenous family described as T-type calcium channels. Furthermore, they do not account for novel calcium channels described in cerebellar granule cells or other types of cells. (Forti, et al (1993) "Functional diversity of L-type calcium channels in rat cerebellar neurons." *Neuron* 10: 437-450; Tottene,et al. (1996). "Functional diversity of P-type and R-type calcium channels in rat cerebellar neurons." *J. Neurosci.* 16: 6353-6363).

Because of the importance of calcium channels in cellular metabolism and human disease, it would be desirable to identify the remaining classes of α_1 subunits, and to develop expression systems for these subunits which would permit the study and characterization of these calcium channels, including the study of pharmacological modulators of calcium channel function. Thus, it is an object of the present invention to provide heretofor undisclosed calcium channels having novel α_1 subunits, including cell lines expressing these

TABLE 1

	ω-conotoxin GVIA	1,4-dihydropyridines	cadmium	ω-agatoxin IVA	ω-conotoxin MVIIC	native Ca^{2+} channel type
α_{1A}	-	-	✓	✓	✓	P/Q-type
α_{1B}	✓	-	✓	-	✓	N-type
α_{1C}	-	✓	✓	-	-	L-type
α_{1D}	-	✓	✓	-	-	L-type
α_{1E}	-	-	✓	-	-	novel
α_{1S}	-	✓	✓	-	-	L-type

new calcium channels. It is a further object of the present invention to provide a method for testing these novel calcium channels using such cell lines.

SUMMARY OF THE INVENTION

The present invention provides sequences for a novel mammalian calcium channel subunits of T-type calcium channels, which we have labeled as α_{1G}, α_{1H} and α_{1I} subunits. Knowledge of the sequences of these calcium channel subunits may be used in the development of probes for mapping the distribution and expression of the subunits in target tissues. In addition, these subunits, either alone or assembled with other proteins, can produce functional calcium channels, which can be evaluated in model cell lines to determine the properties of the channels containing the subunits of the invention. These cell lines can be used to evaluates the affects of pharmaceuticals and/or toxic substances on calcium channels incorporating α_{1G}, α_{1H} and α_{1I} subunits

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A and B show a comparison of the waveforms and current voltage relationship for α_{1G};

Figs. 2A and Bshow a comparison of the waveforms and current voltage relationship for α_{1I} calcium channels.

Fig. 3 shows a comparison of the steady state inactivation profiles of the α_{1G} and α_{1I} calcium channels.

Figs. 4A-C show a comparison of the inactivation kinetics of the α_{1G} and α_{1I} calcium channels.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes the following aspects for which protection is sought:

(a) novel mammalian (including human) calcium channel subunits and DNA sequences encoding such subunits. Specifically, the invention encompasses an at least partially purified DNA molecule comprising a sequence of nucleotides that encodes an α subunit of a T-type calcium channel, and such α subunits *per se*. It will be appreciated that polymorphic variations may be made or may exist in the DNA of some individuals leading to minor deviations in the DNA or amino acids sequences from those shown which do not lead to any substantial alteration in the function of the calcium channel. Such variations, including variations which lead to substitutions of amino acids having similar properties are considered to be within the scope of the present invention. Thus, in one embodiment, the present application claims DNA molecules which encode α_1 subunits of mammalian T-type calcium channels, and which hybridize under conditions of medium (or higher) hybridization stringency with one or another of the specific sequences disclosed in this application. This level of hybridization stringency is generally sufficient given the length of the seqeunces involved to permit recovery of the subunits within the scope of the invention from mammalian DNA libraries.

(b) polynucleotide sequences useful as probes in screening human cDNA libraries for genes encoding these novel calcium channel subunits. These probes can also be used in histological assay to determine the tissue distribution of the novel calcium channel subunits.

(c) at least partially purified α_1 subunits and related peptides for mammalian T-type calcium channels. These proteins and peptides can be used to generate polyclonal or monoclonal antibodies to determine the cellular and subcellular distribution of T-type calcium channel subunits.

(d) eukaryotic cell lines expressing the novel calcium channel subunits. These cell lines can be used to evaluate compounds as pharmacological modifiers of the function of the novel calcium channel subunits.

(e) a method for evaluating compounds as pharmacological modifiers of the function of the novel calcium channel subunits using the cell lines expressing those subunits alone or in combination with other calcium channel subunits.

Further, since defects in the novel calcium channel subunits may be associated with a human genetic disease including, but not limited to; epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome and Parkinson's disease; characterization of such associations and ultimately diagnosis of associated diseases can be carried out with probes which bind to the wild-type or defective forms of the novel calcium channels.

As used in the specification and claims of this application, the term "T-type calcium channel" refers to a voltage-gated calcium channel having a low activation voltage, generally less than -50 mV, and most commonly less than -60 mV. T-type calcium channels also exhibit comparatively negative steady-state inactivation properties and slow deactivation kinetics. The terms "α_1 subunit" or "α_1 calcium channel" refer to a protein subunit of a calcium channel which is responsible for pore formation and contains the voltage sensor and binding sites for calcium channel agonists and antagonists. Such subunits may be independently functional as calcium channels or may require the presence of other subunit types for complete functionality.

As used in the specification and claims of this application, the phrase "at least partially purified" refers to DNA or protein preparations in the which the specified molecule has been separated from adjacent cellular components and molecules with which it occurs in the natural state, either by virtue of performing a physical separation process or by virtue of making the DNA or protein molecule in a non-natural environment in the first place. The term encompasses cDNA molecules and expression vectors.

In accordance with the present invention, we have identified mammalian DNA sequences which code for novel T-type calcium channel α_1 subunits. These subunits are

believed to represent new types of α_1 subunits of mammalian voltage-dependent calcium channels which have been designated as types α_{1G}, α_{1H} and α_{1I}.

The novel α_1 subunits of the invention were identified by screening the *C. elegans* genomic DNA sequence data base for sequences homologous to previously identified mammalian calcium channel α_1 subunits. Specifically, the following twelve mammalian α_1 subunit sequences were used to screen the *C. elegans* genomic data bank:

rat brain α_{1A} : GTCAAAACTC AGGCCTTCTA CTGG	SEQ ID. No. 1
rat brain α_{1A} : AACGTGTTCT TGGCTATCGC GGTG	SEQ ID. No. 2
rat brain α_{1B} : GTGAAAGCAC AGAGCTTCTA CTGG	SEQ ID. No. 3
rat brain α_{1B} : AACGTTTTCT TGGCCATTGC TGTG	SEQ ID. No. 4
rat brain α_{1C} : GTTAAATCCA ACGTCTTCTA CTGG	SEQ ID. No. 5
rat brain α_{1C} : AATGTGTTCT TGGCCATTGC GGTG	SEQ ID. No. 6
rat brain α_{1D} : GTGAAGTCTG TCACGTTTTA CTGG	SEQ ID. No. 7
rat brain α_{1D} : AAGCTCTTCT TGGCCATTGC TGTA	SEQ ID. No. 8
rat brain α_{1E} : GTCAAGTCGC AAGTGTTCTA CTGG	SEQ ID. No. 9
rat brain α_{1E} : AATGTATTCT TGGCTATCGC TGTG	SEQ ID. No. 10
rat brain consensus #1 : ATCTAYGCYR TSATYGGSAT G	SEQ ID. No. 11
rat brain consensus #2 : ATGGACAAYT TYGASTAYTC	SEQ ID. No. 12

This search identified four distinct *C. elegans* cosmids that contain open reading frames (coding regions) that exhibit homology to mammalian calcium channel α_1 subunits:

cosmid and reading frame T02C5.5

cosmid and reading frame C48A7.1

cosmid and reading frame C54D2.5

cosmid and reading frame C27F2.3

Examination of the four *C. elegans* cosmid sequences by phylogeny analysis shows that two of these, T02C5.5 and C48A7.1, correspond closely with previously identified mammalian α_1 subunits. T02C5.5 appears to be an ancestral member related to the mammalian α_{1A}, α_{1B} and α_{1E} subunits. C48A7.1 appears to be an ancestral member related to the mammalian L-type channels encoded by α_{1C}, α_{1D} and α_{1S}. In contrast, the *C. elegans* cosmids C54D2.5 and C27F2.3 identify novel types of calcium channel α_1 subunits distinct from the other mammalian subtypes.

Mammalian counterparts of the *C. elegans* calcium channel α_1 subunit encoded by C54D2.5 were identified by screening of the GenBank expressed sequence tag (EST) data bank. This analysis identified a total of 13 mammalian sequences that exhibit some degree of DNA sequence and amino acid identity to C54D2.5, of which 8 are human sequences. (Table 2) Some of these sequences appear unlikely to encode novel calcium channel subunits because they either exhibit a significant degree of homology to previously identified mammalian α_1 subunits (for example, clones H06096 and H14053) or exhibit homology in a region not considered to be diagnostic of calcium channel α_1 subunits specifically as opposed to other types of ion channel molecules in general (for example, clone D20469). One of the five remaining sequences was evaluated and appears to encode a sodium channel. Four sequences (H55225, H55617, H55223, and H55544), however, encode what are believed to be previously unidentified calcium channel α_1 subunits. For these subunits, the amino acid sequences closely match that of known calcium channel subunits in conserved regions but are sufficiently different to indicate that they do not encode previously identified mammalian calcium channel α_1 subunits, α_{1A}, α_{1B}, α_{1C}, α_{1D}, α_{1E}, or α_{1S}. The expected amino acid sequence closely matches but is not identical to amino acid sequences in these known calcium channel subunits.

Table 2

Query = C54D2.5 CE02562 CALCIUM CHANNEL ALPHA-1 SUBUNIT LG:6

Database: Non-redundant Database of GenBank EST Division
824,500 sequences; 302,742,428 total letter

Sequences producing High-scoring Segment Pairs:		Frame	Score	P(N)
gb|AA183990|AA183990	ms53e02.r1 Life Tech mouse embry...	+1	108	1.8e-24
gb|H55225|H55225	**CHR220164 Homo sapiens genomic c...**	**+1**	**136**	**2.5e-10**
dbj|D68412|CELK131B1F	C.elegans cDNA clone yk131b1 : 5...	+3	117	1.7e-06
gb|R75128|R75128	MDB1075 Mouse brain, Stratagene ...	+3	113	7.2e-06
gb|H55617|H55617	**CHR220556 Homo sapiens genomic c...**	**+2**	**102**	**2.8e-05**
emb|F07776|HSC2HD061	**H. sapiens partial cDNA sequence...**	**+3**	**100**	**0.00057**
gb|W76774|W76774	me84e08.r1 Soares mouse embryo N...	+2	98	0.0012
gb|H06096|H06096	yl77e01.r1 Homo sapiens cDNA clo...	+3	98	0.0015
gb|H14053|H14053	ym65d10.r1 Homo sapiens cDNA clo...	+2	91	0.0036
gb|H55223|H55223	**CHR220162 Homo sapiens genomic c...**	**+2**	**87**	**0.0039**
dbj|D35703|CELK024D9F	C.elegans cDNA clone yk24d9 : 5'...	+3	74	0.046
dbj|D20469|HUMGS01443	Human HL60 3'directed MboI cDNA,...	-2	66	0.91
gb|H55544|H55544	**CHR220483 Homo sapiens genomic c...**	**+1**	**65**	**0.98**

The four sequences (H55225, H55617, H55223, and H55544) are found on human chromosome 22, and are now believed to all be part of the same gene encoding the novel human calcium channel subunit α_{1I}.

The sequences of the four selected sequences and the references from which they are taken are given as follows:

H55225 SOURCE human clone=C22_207 primer=T3 library=Chromosome 22 exon

Trofatter, et al., *Genome Res.* 5 (3): 214-224 (1995)

SEQ ID No. 13

1 GTGATCACTC TGGAAGGCTG GGTGGAGATC ATGTACTACG TGATGGATGC TCACTCCTTC

61 TACAACTTCA TCTACTTCAT CCTGCTTATC ATACCCCTCT TGCCTTGCAC CCCATATGGT

121 CTTCCCAGAG TGAGCTCATC CACCTCGTCA TGCCTGACTC GACGTTCA

H55617 SOURCE human clone=C22_757 primer=T3 library=Chromosome 22 exon

Trofatter, et al., *Genome Res.* 5 (3): 214-224 (1995)

SEQ ID No. 14

1 GATGGTCGAG TACTCCCTGG ACCTTCAGAA CATCAACCTG TCAGCCATCC GCACCGTGCG

61 CGTCCTGAGG CCCCTCAAAG CCATCAACCG CGTGCCCA

H55223 SOURCE human clone=C22_204 primer=T3 library=Chromosome 22 exon

Trofatter, et al, *Genome Res.* 5 (3): 214-224 (1995)

SEQ ID No. 15

1 CATGCTGGTG ATCCTGCTGA ACTGCGTGAC ACTTGGCATG TACCAGCCGT GCGACGACAT

61 GGACTGCCTG TCCGACCGCT GCAAGATCCT GCAG

H55544 SOURCE human clone=C22_651 primer=T3 library=Chromosome 22 exon

Trofatter, et al, *Genome Res.* 5 (3): 214-224 (1995)

SEQ ID No. 16

1 GTATCTCTGG TTACTTTAGT AGCCAACACT CTTGGCTACT CAGACCTTGG TCCCATTAAA

61 TCCCTGCGAA CCTTGAGAGC ACTAAGACCT CTAAGAGCTT TGTCTAGATT TGAAGGAATG

121 AGG

A search of the Sanger Genome Sequencing Center (Cambridge, U.K.) and the Washington University Genome Sequencing Center (St. Louis. MO) sequences in progress revealed a Bacterial Artificial Chromosome (BAC) sequence (bK206c7) that contained matches to the *C. elegans* cosmid open reading frame, C54D2.5, and to the four human

chromosome 22 ESTs, H55225, H55617, H55223,H55544. The C. elegans C54D2.5 cosmid sequence and the human EST sequences were then used to compare the translation of the bK206c7 BAC genomic sequence in all 6 reading frames. The analysis was performed using the graphical program Dotter (Eric Sohnhammer, NCBI). The analysis revealed a series of potential coding regions on one strand of the bK206c7 BAC sequence. These were subsequently translated in all 3 reading frames and the potential splice junctions identified. The translated sequence of this longer DNA fragment which is part of the human α_{II} subunit gene is given by Seq. ID Nos. 17 and 18.

Using the sequence information from the four EST's, a full length gene can be recovered using any of several techniques. Polynucleotide probes having a sequence which corresponds to or hybridizes with the EST sequences or a distinctive portion thereof (for example oligonucleotide probes having a length of 18 to 100 nucleotides) can be used to probe a human cDNA library for identification of the full length DNA encoding the α_{II} subunits. The process of identifying cDNAs of interest using defined probes is well known in the art and is, for example, described in International Patent Publication No. WO95/04144, which is incorporated herein by reference. This process generally involves screening bacterial hosts (e.g. *E. coli*) harboring the library plasmids or infected with recombinant lambda phage with labeled probes, e.g. radiolabeled with ^{32}P, and selection of colonies or phage which bind the labeled probe. Each selected colony or phage is grown up, and the plasmids are recovered. Human cDNAs are recovered from the plasmids by restriction digestion, or can be amplified, for example by PCR. The recovered cDNA can be sequenced, and the position of the calcium channel subunit-encoding region further refined, although neither process is not necessary to the further use of the cDNA to produce cell lines expressing the novel calcium channel subunits.

Longer portions of DNA-encoding the novel calcium channel subunits of the invention can also be recovered by PCR cloning techniques using primers corresponding to or based upon the EST sequences. Using this technique to identify relevant sequences within a human

brain total RNA preparation confirmed that the novel α_{1I} calcium channel subunit is present in human brain. Subcloning of the 567 nt PCR product (Seq. ID No. 19, amino acids Seq. ID No. 20) and subsequent sequencing thereof showed that this product corresponds to the derived sequence form the bK206c7 BAC genomic sequence, the nucleotide sequence of which is given as SEQ ID No. 17 (amino acid sequence Seq. ID No. 18). The same experiment was performed using a rat brain RNA preparation and resulted in recovery of a substantially identical PCR product. (SEQ ID. No. 21). The protein encoded by the rat PCR product (SEQ ID No. 22) is 96% identical to the human PCR product (Seq. ID No. 20).

These sequences, which encode a partial subunit can be used as a basis for constructing full length human or rat α_{1I} clones. Briefly, the subcloned α_{1I} PCR product is radiolabeled by random hexamer priming according to standard methods (See, Sambrook , J., Fritsch, E.F. and Maniatis, T. (1989) *Molecular Cloning, A Laboratory Manual.* Cold Spring Harbor Press) and used to screen commercial human brain cDNA libraries (Stratagene, La Jolla, CA). The screening of cDNA libraries follows standard methods and includes such protocols as infecting bacteria with recombinant lambda phage, immobilizing lambda DNA to nitrocellulose filters and screening under medium hybridization stringency conditions with radiolabeled probe. cDNA clones homologous to the probe are identified by autoradiography. Positive clones are purified by sequential rounds of screening.

Following this protocol, most purified cDNA's are likely to be partial sequence clones due the nature of the cDNA library synthesis. Full length clones are constructed from cDNA's which overlap in DNA sequence. Restriction enzyme sites which overlap between cDNAs are used to ligate the individual cDNA's to generate a full-length cDNA. For subsequent heterologous expression, the full-length cDNA is subcloned directly into an appropriate vertebrate expression vector, such as pcDNA-3 (Invitrogen, San Diego, CA) in which expression of the cDNA is under the control of a promoter such as the CMV major intermediate early promoter/enhancer. Other suitable expression vectors include, for example, pMT2, pRC/CMV, pcDNA3.1 and pCEP4.

Following these protocols, as described more fully in Example 4, full length mammalian α_{1G}, α_{1H} and α_{1I} calcium channel subunit cDNAs were isolated by using the 567 base pair human fragment (Seq. ID No. 19) to screen a rat brain cDNA library. Sequencing of the recovered sequences identified the three distinct classes of calcium channel subunits which have been demoninated herein as α_{1G}, α_{1H} and α_{1I} subunits. For each class of subunit, complete sequencing of the largest cDNA confirmed that it represented only a portion of the predicted calcium channel coding region. Complete sequences for the three new subunits were obtained by rescreening the rat brain cDNA library with probes derived from the partial length cDNAs to obtain overlapping segments. These segments were combined to form a complete gene by restriction digestion and ligation. The complete cDNA sequences of the rat α_{1G}, α_{1H} and α_{1I} subunits are given by Sequence ID Nos. 23, 25 and 27, respectively. Corresponding amino acid sequences are given by Sequence ID Nos. 24, 26 and 28. The same techniques are employed to recover human sequences by screening of a human or other mammalian library. Thus, for example, partial length human sequences for α_{1G} and α_{1H} T-type calcium channels have been recovered using the same probe (Seq. ID No. 19) and the full length rat α_{1I} cDNA (Seq. ID. No. 27) has been used to recover a partial length DNA encoding a human α_{1I} T-type calcium channel. The DNA and amino acid sequences for these partial length human calcium channels are given by Seq. ID Nos. 30-35.

Once the full length cDNA is cloned into an expression vector, the vector is then transfected into a host cell for expression. Suitable host cells include *Xenopus* oocytes or mammalian cells such as human embryonic kidney cells as described in International Patent Publication No. WO 96/39512 which is incorporated herein by reference and Ltk cells as described in US Patent No. 5,386,025 which is incorporated herein by reference. Transfection into host cells may be accomplished by microinjection, lipofection, glycerol shock, electroporation calcium phosphate or particle-mediated gene transfer. The vector may also be transfected into host cells to provide coexpression of the novel α_1 subunits with a β and/or an $\alpha_2\delta$ subunit.

To confirm that the three full length cDNAs (sequence ID Nos. 23, 25 and 27) encoded function calcium channels, the α_{1G} and α_{1I} cDNAs were transiently transfected into human embryonic kidney cells and evaluated using electrophysiological recording techniques. As described in more detail in Example 5 below, and as illustrated in Figs. 1-4), the results are consistent with a role of these subunits in native T-type channels in nerve, muscle and endocrine cells.

The resulting cell lines expressing functional calcium channels including the novel α_1 subunits of the invention can be used test compounds for pharmacological activity with respect to these calcium channels. Thus, the cell lines are useful for screening compounds for pharmaceutical utility. Such screening can be carried out using several available methods for evaluation of the interaction, if any, between the test compound and the calcium channel. One such method involves the binding of radiolabeled agents that interact with the calcium channel and subsequent analysis of equilibrium binding measurements including but not limited to, on rates, off rates, K_d values and competitive binding by other molecules. Another such method involves the screening for the effects of compounds by electrophysiological assay whereby individual cells are impaled with a microelectrode and currents through the calcium channel are recorded before and after application of the compound of interest. Another method, high-throughput spectrophotometric assay, utilizes the loading the cell lines with a fluorescent dye sensitive to intracellular calcium concentration and subsequent examination of the effects of compounds on the ability of depolarization by potassium chloride or other means to alter intracellular calcium levels. Compounds to be tested as agonists or antagonists of the novel α_{1I} calcium channel subunits are combined with cells that are stably or transiently transformed with a DNA sequence encoding the α_{1G}, α_{1H} and α_{1I} calcium channel subunits of the invention and monitored using one of these techniques.

DNA fragments with sequences given by SEQ ID Nos. 13-17 and 19, or polynucleotides with the complete coding sequences as given by Sequence ID Nos. 23, 25 and 27 or distinctive portions thereof which do not exhibit non-discriminatory levels of homology

with other types of calcium channel subunits may also be used for mapping the distribution of α_{1G}, α_{1H} and α_{1I} calcium channel subunits within a tissue sample. This method follows normal histological procedures using a nucleic acid probe, and generally involves the steps of exposing the tissue to a reagent comprising a directly or indirectly detectable label coupled to a selected DNA fragment, and detecting reagent that has bound to the tissue. Suitable labels include fluorescent labels, enzyme labels, chromophores and radio-labels.

EXAMPLE 1

In order to isolate novel human calcium channel α_1 subunits using standard molecular cloning protocols, synthetic DNA probes are prepared, radiolabeled with ^{32}P and utilized to screen human cDNA libraries commercially available in lambda phage vectors (Stratagene, La Jolla, CA) based on the human DNA sequences for H55225, H55617, H55223, and H55544. DNA fragments with the sequence of sequence ID Nos 17 and 19 may also be used for this purpose. Positive phage are purified through several rounds of screening involving immobilizing the phage DNA on nitrocellulose filters, hybridizing with the radiolabeled probe, washing off of excess probe and then selection of clones by autoradiography. Clones identified by this approach are expected to be partial length clones due to the nature of cDNA library synthesis and several rounds of screening for each calcium channel type may be necessary to obtain full-length clones.

To characterize the clones, double stranded plasmid DNA is prepared from the identified clones and the sequences are determined using ^{35}S dATP, Sequenase and standard gel electrophoresis methods. Regions of similarity and regions of overlap are determined by comparison of each cDNA sequence.

Full-length clones are constructed by ligating overlapping cDNA fragments together at common restriction enzyme sites. The full-length clones are subsequently inserted into vectors suitable for expression in vertebrate cells (e.g. pMT2, pRC/CMV, pcDNA3.1, pCEP4,

pREP7) by ligation into restriction sites in the vector polylinker region which is downstream of the promoter used to direct cDNA expression.

DNA encoding the novel calcium channels can be stably or transiently introduced into eukaryotic cells (e.g. human embryonic kidney, mouse L cells, chinese hamster ovary, etc) by any number of available standard methods. Stable transfection is achieved by growing the cells under conditions that promote growth of cells expressing a marker gene which is contained in the expression vector (e.g. dihydrofolate reductase, `thymidine kinase, or the like). The heterologous DNA encoding the human calcium channel may be integrated into the genome or may be maintained as an episomal element.

Expression of the human calcium channel in transfected cells may monitored by any number of techniques, including Northern blot for RNA analysis, Southern blot for cDNA detection, electrophysiological assay for calcium channel function, the binding of radiolabeled agents thought to interact with the calcium channel, and fluorescent assay of dyes sensitive to intracellular calcium concentration.

EXAMPLE 2

Heterologous Expression of Mammalian α_{1I} Calcium Channels in Cells

A. Transient Transfection in Mammalian Cells

Host cells, such as human embryonic kidney cells, HEK 293 (ATCC# CRL 1573) are grown in standard DMEM medium supplemented with 2 mM glutamine and 10% fetal bovine serum. HEK 293 cells are transfected by a standard calcium-phosphate-DNA co-precipitation method using a full-length mammalian α_{1I} calcium channel cDNA (for example, Seq. ID. No. 27) in a vertebrate expression vector (for example see Current protocols in Molecular Biology). The α_{1I} calcium channel cDNA may be transfected alone or in combination with other cloned subunits for mammalian calcium channels, such as $\alpha 2\delta$ and β subunits, and also with clones for marker proteins such the jellyfish green fluorescent protein.

Electrophysiological Recording: After an incubation period of from 24 to 72 hrs the culture medium is removed and replaced with external recording solution (see below). Whole cell patch clamp experiments are performed using an Axopatch 200B amplifier (Axon Instruments, Burlingame, CA) linked to an IBM compatible personal computer equipped with pCLAMP software. Microelectrodes are filled with 3 M CsCl and have typical resistances from 0.5 to 2.5 MΩ. The external recording solution is 20 mM $BaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 40 mM TEACl, 10 mM Glucose, 65 mM CsCl, (pH 7.2). The internal pipette solution is 105 mM CsCl, 25 mM TEACl, 1 mM $CaCl_2$, 11 mM EGTA, 10 mM HEPES (pH 7.2). Currents are typically elicited from a holding potential of -100 mV to various test potentials. Data are filtered at 1 kHz and recorded directly on the harddrive of a personal computer. Leak subtraction is carried out on-line using a standard P/5 protocol. Currents are analyzed using pCLAMP versions 5.5 and 6.0. Macroscopic current-voltage relations are fitted with the equation $I = \{1/(1+\exp(-(V_m-V_h)/S)\} \times G - (V_m-E_{rev})$, where V_m is the test potential, V_h is the voltage at which half of the channels are activated, and S reflects the steepness of the activation curve and is an indication of the effective gating charge movement. Inactivation curves are normalized to 1 and fitted with $I = (1/1 + \exp((V_m-V_h)/S)$ with V_m being the holding potential. Single channel recordings are performed in the cell-attached mode with the following pipette solution (in mM): 100 $BaCl_2$, 10 HEPES, pH 7.4 and bath solution: 100 KCl, 10 EGTA, 2 $MgCl_2$, 10 HEPES, pH 7.4.

B. Transient Transfection in Xenopus Oocytes

Stage V and VI Xenopus oocytes are prepared as described by Dascal et al (1986), Expression and modulation of voltage-gated calcium channels after RNA injection into Xenopus oocytes. Science 231:1147-1150. After enzymatic dissociation with collagenase, oocytes nuclei are microinjected with the human α_{1I} calcium channel cDNA expression vector construct (approximately 10 ng DNA per nucleus) using a Drummond nanoject apparatus. The α_{1I} calcium channel may be injected alone, or in combination with other mammalian

calcium channel subunit cDNAs, such as the α2-δ and β1b subunits. After incubation from 48 to 96 hrs macroscopic currents are recorded using a standard two microelectrode voltage-clamp (Axoclamp 2A, Axon Instruments, Burlingame, CA) in a bathing medium containing (in mM): 40 $Ba(OH)_2$, 25 TEA-OH, 25 NaOH, 2 CsOH, 5 HEPES (pH titrated to 7.3 with methan-sulfonic acid). Pipettes of typical resistance ranging from 0.5 to 1.5 mΩ are filled with 2.8M CsCl, 0.2M CsOH, 10mM HEPES, 10mM BAPTA free acid. Endogenous Ca (and Ba) -activated Cl currents are suppressed by systematically injecting 10-30 nl of a solution containing 100mM BAPTA-free acid, 10mM HEPES (pH titrated to 7.2 with CsOH) using a third pipette connected to a pneumatic injector. Leak currents and capacitive transients are subtracted using a standard P/5 procedure.

EXAMPLE 3

Construction of Stable Cell Lines Expressing Mammalian α_{1I} Calcium Channels

Mammalian cell lines stably expressing human α_{1I} calcium channels are constructed by transfecting the α_{1I} calcium channel cDNA into mammalian cells such as HEK 293 and selecting for antibiotic resistance encoded for by an expression vector. Briefly, a full-length mammalian α_{1I} calcium channel cDNA (for example Seq. ID No. 27) subcloned into a vertebrate expression vector with a selectable marker, such as the pcDNA3 (InvitroGen, San Diego, CA), is transfected into HEK 293 cells by calcium phosphate coprecipitation or lipofection or electroporation or other method according to well known procedures (Methods in Enzymology, Volume 185, Gene Expression Technology (1990) Edited by Goeddel, D.V.). The α_{1I} calcium channel may be transfected alone, or in combination with other mammalian calcium channel subunit cDNAs, such as the α2-δ and β1b subunits, either in a similar expression vector or other type of vector using different selectable markers. After incubation for 2 days in nonselective conditions, the medium is supplemented with Geneticin (G418) at a concentration of between 600 to 800 ug/ml. After 3 to 4 weeks in this medium, cells which are resistant to G418 are visible and can be cloned as isolated colonies using standard cloning

rings. After growing up each isolated colony to confluency to establish cell lines, the expression of α_{1I} calcium channels can be determined at with standard gene expression methods such as Northern blotting, RNase protection and reverse-transcriptase PCR.

The functional detection of α_{1I} calcium channels in stably transfected cells can be examined electrophysiologically, such as by whole patch clamp or single channel analysis (see above). Other means of detecting functional calcium channels include the use of radiolabeled ^{45}Ca uptake, fluorescence spectroscopy using calcium sensitive dyes such as FURA-2, and the binding or displacement of radiolabeled ligands that interact with the calcium channel.

EXAMPLE 4

In order to recover full-length mammalian sequences for novel calcium channels, the 567 base pair partial length human brain α_{1I} cDNA was gel-purified, radio-labelled with ^{32}P dATP and dCTP by random priming (Feinberg et al., 1983, *Anal. Biochem.* 132: 6-13) and used to screen a rat brain cDNA library constructed in the phase vector Lambda Zapp II. (Snutch et al., 1990, *Proc Natl Acad Sci (USA)* 87: 3391-3395). Screening was carried out at 62°C in 5XSSPE (1XSSPE= 0.18 M NaCl; 1mM EDTA; 10 mM sodium phosphate, pH=7.4 0.3% SDS, 0.2 mg/ml denatured salmon sperm DNA). Filters were washed at 62°C in 0.2X SSPE/0.1% SDS. After three rounds of screening and plaque purification, positive phages were transformed into Bluescript phagemids (Stratagene, La Jolla, CA) by *in vivo* excision.

Double stranded DNA sequencing on the recombinant phagemids was performed using a modified dideoxynucleotide protocol (Biggin et al., 1983, *Proc Natl Acad Sci (USA)* 80:3963-3965) and Sequenase version 2.1 (United States Biochemical Corp.). DNA sequencing identified three distinct classes of calcium channel α_1 subunits: designated as α_{1G}, α_{1H} and α_{1I} calcium channel subunits.

For each class of calcium channel α_1 subunit, the largest cDNA was completely sequenced and determined to represent only a portion of the predicted calcium channnel

coding region. In order to isolate the remaining portions of α_{1G} and α_{1I} calcium channel subunits, the α_{1G} clone was digested with HindIII and SpeI. The resulting 540 base pair fragment was gel purified, radiolabeled with ^{32}P dATP and dCTP by random priming and used to rescreen the rat brain cDNA library as described above. The sequence of the 540 base pair α_{1G} screening probe used is given by Seq. ID No. 29. Other sequences spanning regions of distinctiveness within the sequences for the subunits could also be employed.

Double-stranded DNA sequencing of the purified recombinant phagemids showed that additional α_{1G}, α_{1H} and α_{1I} calcium channel subunit cDNAs overlapped with the original partial length cDNAs and together encoded complete protein coding regions as well as portions of their respective 5' and 3' non-coding untranslated regions.

To recover further human sequences for the novel α_{1G} and α_{1H} calcium channels, the 567 base pair partial length human brain α_{1I} cDNA (Seq. 19) was radio-labelled with ^{32}P dATP and dCTP by random priming and used to screen a commercial human thalamus cDNA library (Clontech). Hybridization was performed overnight at 65 °C in 6 X SSPE; 0.3% SDS; 5X Denhardt's. Filters were washed at 65 °C in 0.1 X SSPE/ 0.3% SDS. After four rounds of screening and plaque purification, positive phages were selected, DNA prepared and the insert cDNA excised form the lambda vector by digestion with Eco R1 restriction enzyme. The excised cDNA was subcloned into the plasmid Bluescript KS (Stratagene, La Jolla, CA) and the DNA sequence determined using a modified dideoxynucleotide protocol and Sequenase version 2.1. The partial length α_{1G} cDNA isolated consisted of 2212 base pairs of which 279 base pairs were 5' noncoding and 1,933 base pairs were coding region representing 644 amino acids (Seq. ID Nos. 30, 31). The partial α_{1H} cDNA isolated consisted of 1,608 base pairs of which 53 base pairs were 5' noncoding and 1,555 were coding region representing 518 amino acids (Seq. ID Nos. 32, 33).

To recover further human sequences for the novel α_{1I} calcium channel, the full-length rat brain α1I cDNA (Seq. 27) was radio-labelled ^{32}P dATP and dCTP by random priming and used to screen a commercial human hippocampus cDNA library (Stratagene). Hybridization

was performed overnight at 65 °C in 6 X SSPE; 0.3% SDS; 5X Denhardt's. Filters were washed at 65 °C in 0.1 X SSPE/ 0.3% SDS. After four rounds of screening and plaque purification, positive phages were transformed into Bluescript phagemids (Stratagene, LA Jolla, CA) by *in vitro* excision. The excised cDNA DNA sequence was determined using a modified dideoxynucleotide protocol and Sequenase version 2.1. The partial α_{1I} cDNA isolated consisted of 1,080 base pairs of coding region representing 360 amino acids (Seq. ID Nos. 34, 35).

EXAMPLE 5

Double-stranded DNA sequencing of the purified recombinant phagemids showed that additional α_{1G} and α_{1I} calcium channel cDNAs overlapped with the original partial length cDNAs and together encoded complete protein coding regions as well as portions of their respective 5' and 3' non-coding untranslated regions. (Seq. ID Nos. 23 and 27, respectively) In addition to the α_{1G} and α_{1I} calcium channel classes, DNA sequencing of the recombinant phagemids also identified a third class of calcium channel α_1 subunit: designated as the α_{1H} calcium channel subunit. The partial length α_{1H} calcium channel cDNAs overlapped and together encoded a complete α_{1H} coding region as well as portions of the 5' and 3' untranslated regions (Seq. ID. No. 25).

Electrophysiological studies were performed on transiently-transfected human embryonic kidney cells (HEK-tsa201) prepared using the general protocol of Example 2. Transfection was carried out by standard calcium phosphate precipitation. (Okayama et al., 1991, *Methods in Molec. Biol.*, Vol. 7, ed. Murray, E.J.). For maintenance, HEK-tsa201 cells were cultured until approximately 70% confluent, the media removed and cells dispersed with trypsin and gentle trituration. Cells were then diluted 1:10 in culture medium (10% FBS, DMEM plus L-glutamine, pen-strp) warmed to 37°C and plated onto tissue culture dishes. For transient transfection, 0.5 mM $CaCl_2$ was mixed with a total of 20 µg of DNA (consisting of 3µg of either rat brain α_{1G} or α_{1I} calcium channel cDNA, 2 µg of CD8 plasmid marker, and

15 μg of Bluescript plasmid carrier DNA). The DNA mixture was mixed thoroughly and then slowly added dropwise to 0.5 ml of 2 times HeBS (274 mM NaCl, 20mM D-glucose, 10mM KCl, 1.4 mM Na_2HPO_4, 40 mM Hepes (pH=7.05). After incubation at room temperature for 20 min, 100 μl of the DNA mixture was slowly added to each dish of HEK-tsa201 cells and then incubated at 37°C for 24 to 48 hours in a tissue culture incubator (5% CO_2).

Positive transfectant cells were identified visually by addition of 1 μl of mouse CD8 (Lyt2) Dynabeads directly to the recording solution and gentle swirling to mix. Whole cell patch clamp readings were carried out with an Axopatch 200A amplifier (Axon Instruments) as described previously. (Zamponi et al., 1997, *Nature* 385: 442-446). The external recording solution was 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 40 mM TEA-Cl, 10 mM glucose, 92 mM CsCl, pH=7.2 with TEA-hydroxide. The internal pipette solutions was 105 mM CsCl, 25 mM TEA-Cl, 1mM $CaCl_2$, 11 mM EGTA, 10 mM HEPES, pH 7.2 with NaOH.

For determination of current-voltage (I-V) relationships, cells were held at a resting potential of -100 mV and then stepped to various depolarizing test potentials. For steady-state inactivation, cells were held at varius potentials for 20 sec. and currents recorded during a subsequent test pulse to the peak potential of the I-V. Leak currents and capacitative transients were subtracted using a P/5 procedure.

Figs. 1-4 show the results obtained for HEK cells transfected with and expressing the cDNA of sequences ID Nos. 23 and 27, which correspond to the subunits designated as α_{1G} and α_{1I}. Figs. 1A and B and 2A and B shows a comparison of the waveforms and current-voltage relationship for the two channel subunit types. In the presence of recording solution containing 2mM Ca^{2+}, both the α_{1G} and α_{1I} channel subunits exhibit activation properties consistent with native T-type calcium currents. Figs 1 A and 2A show the subunit calcium current from a cell held at -120 mV and depolarized to a series of test potentials. Figs 1B and 2B show the magnitude of the calcium current. From a holding potential of -110 mV, both channel first activate at approximately -70 mV and peak currents are obtained between -40 and -50 mV. Upon depolarization to various test potentials, the current waveforms of the α_{1G}

and α_{1I} calcium channels exhibit an overlapping pattern characteristic of native T-type channels in nerve, muscle and endocrine cells.

Fig. 3 shows steady-state inactivation profiles for the α_{1G} and α_{1I} calcium channels in HEK 293 cells transiently transformed with full length cDNAs (SEQ ID Nos 23 or 27) for α_{1G} or α_{1I} subunits. Steady state inactivation properties were determined by stepping from -120 mV to prepulse holding potentials between -120 mV and -50 mV for 15 sec.. prior to a test potential of -30 mV. The data are plotted as nnormalized whole cell current versus prepulse holding potential and show that α_{1G} exhibits a V_{50} of approximately -85 mV and α_{1I} a V_{50} of approximately -93 mV. Thus, consistent with native T-type calcium channels, both of the α_{1G} and α_{1I} calcium channels exhibit pronounced steady-state inactivation at negative potentials.

Figs. 4A-C show a comparison of the voltage-dependent deactivation profiles of the α_{1G} and α_{1I} calcium channels. KEK 293 cells were transiently transfected with either an α_{1G} or α_{1I} subunit cDNA (Seq. ID No. 23 or 27). The deactivation properties of α_{1G} were determined by stepping from a holding potential of -100 mV to -40mV for 9 msec, and then to potentials between -120 mV and -45 mV. The deactivation properties of α_{1I} were determined by stepping from a holding potential of -100 mV to -40 mV for 20 msec, and then to potentials between -120 mV and -45 mV. Both channels exhibit slow deactivation kinetics compared to typical high-threshold channels, and is consistent with the α_{1G} and α_{1I} subunits being subunits for T-type calcium channels

What is claimed is:

1. An at least partially purified DNA molecule comprising a sequence of nucleotides that encodes an α_1 subunit of a mammalian T-type calcium channel.

2. The DNA molecule of claim 1, wherein the sequence of nucleotides is selected from sequences of nucleotides encoding a protein including the sequence of amino acids set forth in SEQ ID. No. 18, 20, 24, 26, 28, 31, 33, or 35 and sequences of nucleotides that hybridize under conditions of medium hybridization stringency to DNA encoding a protein including the sequence set forth in SEQ ID No. 18, 20, 24, 26, 28, 31, 33, 35.

3. The DNA molecule of Claim 1, wherein the calcium channel is a human calcium channel.

4. The DNA molecule of claim 1, further comprising a promoter region effective to promote expression of the α_1 subunit of a mammalian T-type calcium channel when the DNA molecule is transfected into a vertebrate cell.

5. The DNA molecule of claim 1, having the sequence as set forth in Seq. ID. No. 23, 25 or 27.

6. The DNA molecule of claim 1, wherein the molecule comprises a region consisting of the sequence as set forth in Seq. ID. No. 30, 32 or 34.

7. An at least partially purified α_1 subunit of a mammalian T-type calcium channel.

8. The α_1 subunit of claim 7 , wherein the subunit has the sequence as set forth in Seq. ID No. 24, 26 or 28 .

9. The α_1 subunit of claim 7 , wherein the subunit comprises a region consisting of the sequence as set forth in Seq. ID. No. 31, 33 or 35.

10. A eukaryotic cell transiently or stably transformed with the vertebrate expression vector comprising a sequence of nucleotides that encodes an α_1 subunit of a mammalian T-type calcium channel, wherein the cell expresses the α_1 subunit of a mammalian T-type calcium channel.

11. The cell of claim 10 , wherein the sequence of nucleotides is selected from sequences of nucleotides encoding a protein including the sequence of amino acids set forth in SEQ ID. No. 18, 20, 24, 26, 28, 31, 33, or 35, and sequences of nucleotides that hybridize under conditions of medium hybridization stringency to DNA encoding a protein including the sequence set forth in SEQ ID No. 18, 20, 24, 26, 28, 31, 33, or 35.

12. The cell of claim 10 , wherein the calcium channel is a human calcium channel.

13. The cell of claim 10 , wherein the sequence of nucleotides has the sequence as set forth in Seq. ID. No. 23, 25 or 27 .

14. The cell of claim 10 , wherein the sequence of nucleotides comprises a region consisting of the sequence as set forth in Seq. ID. No. 30, 32 or 34.

15. The cell of claim 10 , wherein the sequence of nucleotides has the sequence as set forth in Seq. ID. No. 27.

16. The cell of claim 10 , wherein the cell is further transformed with and expresses an $\alpha 2\delta$ or a β calcium channel subunit, or both.

17. A eukaryotic cell transiently or stably transformed with a heterologous DNA fragment comprising a sequence of nucleotides that encodes an α_1 subunit of a mammalian T-type calcium channel, wherein the cell expresses the α_1 subunit of a mammalian T-type calcium channel.

18. The cell of claim 17 , wherein the cell is further transformed with and expresses an $\alpha 2\delta$ or a β calcium channel subunit, or both.

19. A method for the production of an α-$_1$ subunit of a mammalian T-type calcium channel comprising, culturing a cell transiently or stably transformed or transfected with DNA encoding the calcium channel subunit under conditions such that the DNA is expressed and the α-$_1$ subunit is produced.

20. A process for producing a eukaryotic cell that is transiently or stably transformed and expresses a mammalian T-type calcium channel, comprising the step of introducing RNA or DNA encoding an α_1 subunit of a mammalian T-type calcium channel.

21. A method of identifying compounds capable of acting as agonists or antagonists for T-type mammalian calcium channels, comprising contacting a recombinant cell expressing a heterologous α_1 subunit of a mammalian T-type calcium channel, with an agent to be tested, and evaluating the interaction, if any, between the agent to be tested and the calcium channel.

22. An isolated DNA fragment having the sequence given by SEQ ID No. 19, 27 or 29.

23. A method for mapping the distribution of T-type calcium channels within a tissue sample comprising the steps of exposing the tissue to a reagent comprising a directly- or indirectly-detectable label coupled to a DNA fragment comprising a sequence selected from among those sequences given by SEQ ID Nos. 13-17, 19, 23, 25, 27, 29, 30, 32 and 34, and detecting reagent that has bound to the tissue.

24. A DNA fragment comprising a sequence of oligonucleotide that encodes a calcium channel, wherein the sequence of nucleotides is selected from sequences of nucleotides encoding a protein including the sequence of amino acids set forth in SEQ ID. No. 18, 20, 24, 26, 28, 31, 33, or 35, or a nucleotide sequence obtainable by subcloning a PCR product of SEQ ID Nos: 13, 14, 15, or 16, labeling it by random hexamer priming, using the primer to screen a commercial human brain cDNA library to produce partial sequence clones containing overlapping cDNAs and ligating cDNAs obtained to produce full length cDNA encoding a calcium channel protein.

ABSTRACT OF THE DISCLOSURE

Sequences and partial sequences for three types of mammalian (human and rat sequences identified) T-type calcium channel subunits which we have labeled as the α_{1G}, α_{1H} and α_{1I} subunits are provided. Knowledge of the sequence of these calcium channel permits the localization and recovery of the complete sequence from human cells, and the development of cell lines which express the novel calcium channels of the invention. These cells may be used for identifying compounds capable of acting as agonists or antagonists to the calcium channels.

NMED.P-001-2
PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Snutch et al.

Serial No.: to be assigned

Filed: herewith

For: NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

Statement Regarding Sequence Listing

Asst. Commissioner for Patents

Washington, D.C. 20231

Sir:

The undersigned hereby certifies that the paper copy of the sequence listing and the machine readable diskette filed herewith contain the same information.

Respectfully submitted,

Marina T. Larson
PTO Reg. No. 32,038
Attorney for Applicant
(970) 668-2050

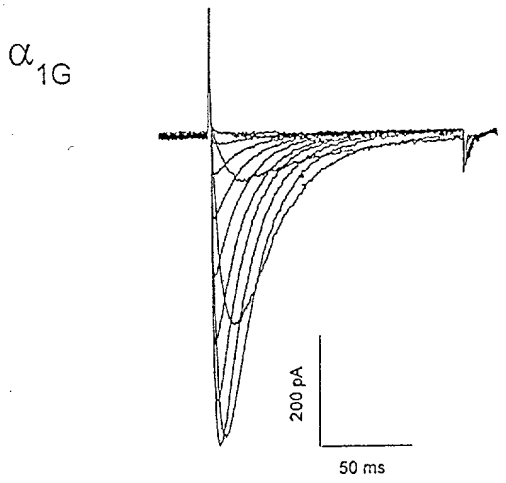

Fig. 1A

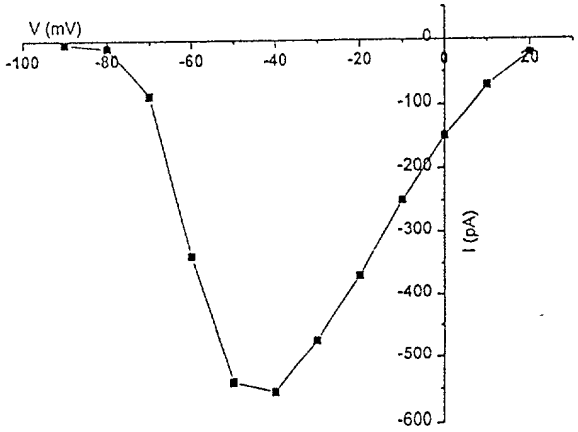

Fig. 1B

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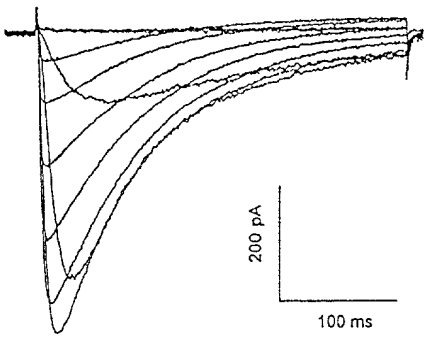


Fig. 2A

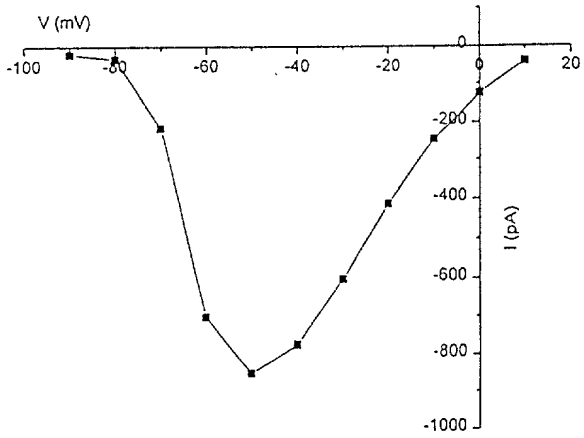


Fig. 2 B

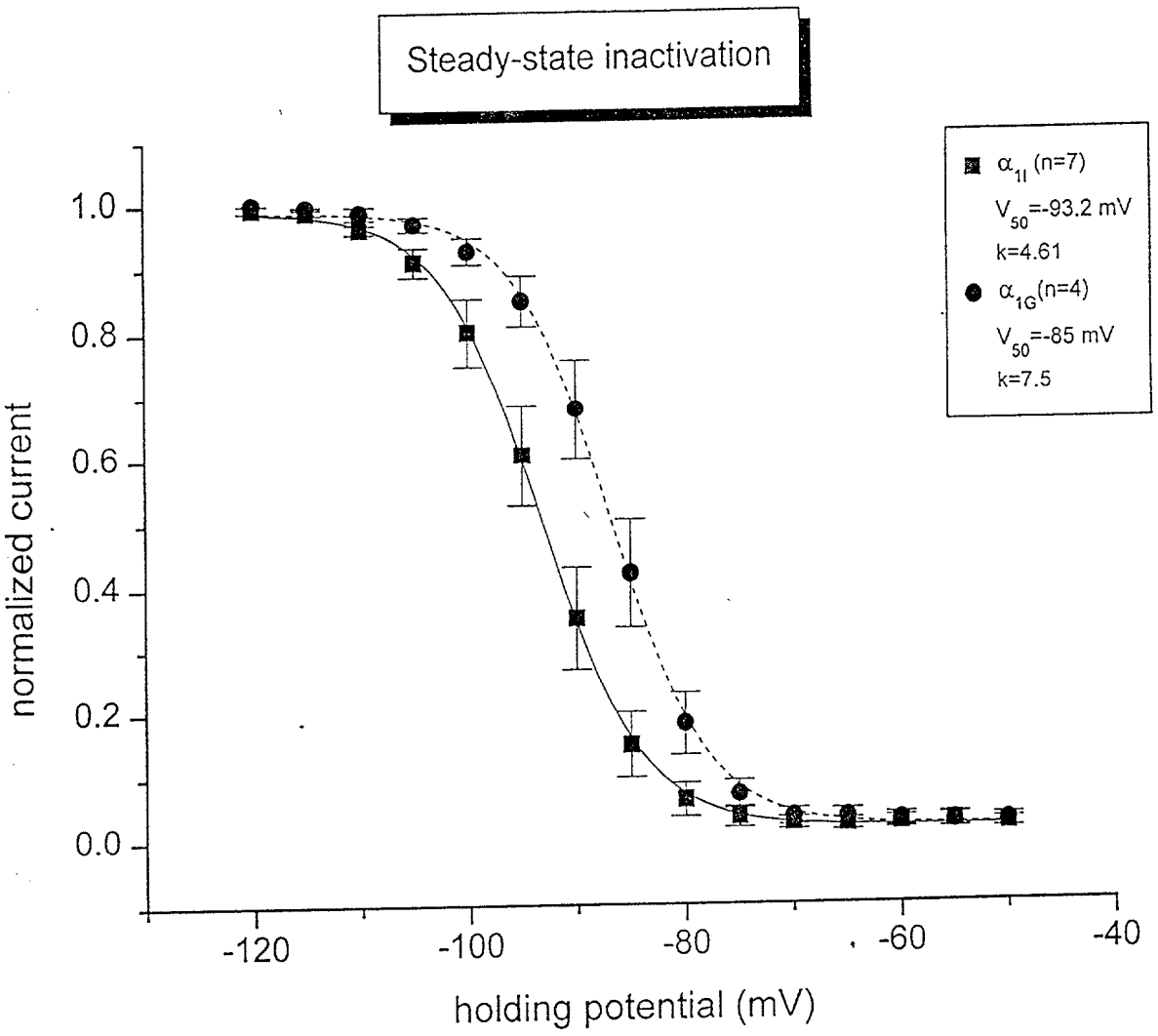

Steady-state inactivation
α_{1I} (n=7)
V_{50}=-93.2 mV
k=4.61
α_{1G}(n=4)
V_{50}=-85 mV
k=7.5
normalized current
1.0
0.8
0.6
0.4
0.2
0.0
-120
-100
-80
-60
-40
holding potential (mV)

Fig. 3

Deactivation

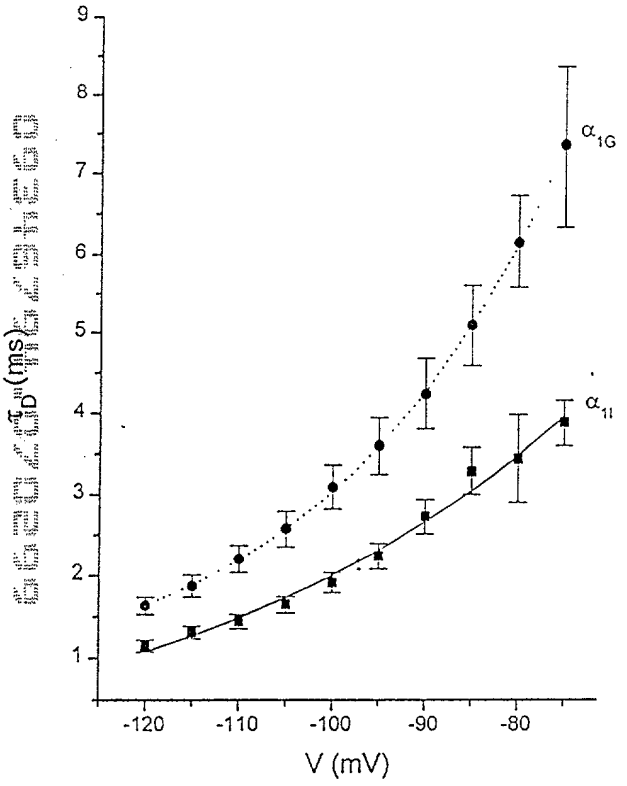
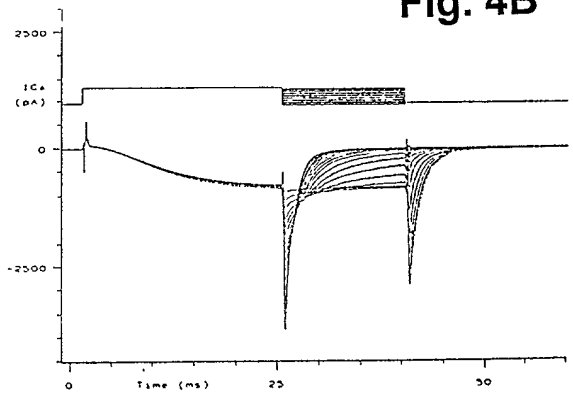


Fig. 4A

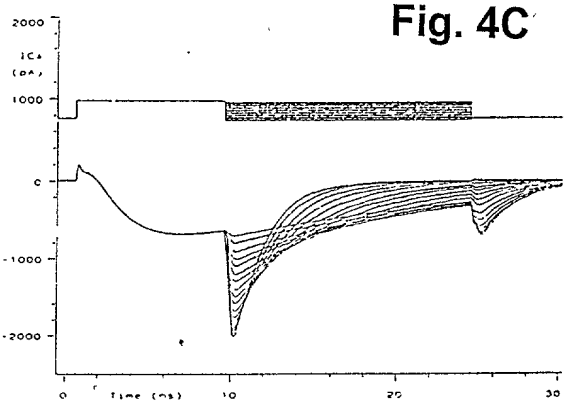
α_{1I}

Fig. 4B



α_{1G}

Fig. 4C



SEQUENCE LISTING

<110> Snutch, Terry P.
Baillie, David L.

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Gln Ala Leu Lys Gln Leu Met Phe Lys Leu Val Ala Thr Val Ala Arg
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Thr His Ala Thr Pro Ser His Ile Thr Gly Gly Pro Gly Thr Gly Met
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His Thr Gly Thr Phe Gln Glu Gly Ala Glu Pro Gly Ser Ser Gln His
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Lys Ala Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Asn Leu Leu
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Ile Pro Pro Leu Lys Glu Gln Gly Arg Glu Cys Cys Leu Ser Lys Asp
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Asp Val Tyr Asp Phe Gly Ala Gly Arg Gln Asp Leu Asn Ala Ser Gly
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Leu Cys Val Asn Trp Asn Arg Tyr Tyr Asn Val Cys Arg Thr Gly Ser
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Ala Asn Pro His Lys Gly Ala Ile Asn Phe Asp Asn Ile Gly Tyr Ala
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Trp Ile Val Ile Phe Gln Val Ile Thr Leu Glu Gly Trp Val Glu Ile
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Leu Thr Gln Glu Asp Trp Asn Val Val Leu Tyr Asn Gly Met Ala Ser
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Thr Ser Pro Trp Ala Ser Leu Tyr Phe Val Ala Leu Met Thr Phe Gly

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Gln Ala Glu Val Thr Val Val Leu Ala Glu Glu Ala Pro Pro Gln Gly
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Leu Arg Lys Thr Gly Arg Gly Arg Gly Gly Leu Asp Gly Gly Gly Leu
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Gln Phe Lys Leu Leu Ala Gly Asn Leu Ser Leu Lys Glu Gly Val Ala
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Asp Glu Val Gly Asp Ala Asn Arg Ser Tyr Ser Asp Glu Asp Gln Ser
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Ser Ser Asn Ile Glu Glu Phe Asp Lys Leu Gln Glu Gly Leu Asp Ser
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Ser Gly Asp Pro Lys Leu Cys Pro Ile Pro Met Thr Pro Asn Gly His
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Leu Asp Pro Ser Leu Pro Leu Gly Gly His Leu Gly Pro Ala Gly Ala
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Ala Gly Pro Ala Pro Arg Leu Ser Leu Gln Pro Asp Pro Met Leu Val
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Ala Leu Gly Ser Arg Lys Ser Ser Val Met Ser Leu Gly Arg Met Ser
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Tyr Asp Gln Arg Ser Leu Val Gly Gly Leu Arg Ala Thr Ala Gly Val
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Gln Ala Ala Phe Gly His Leu Val Pro Gln Pro Trp Val Cys Leu Trp
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Gly Ala Asp Pro Asn Gly Asn Ser Phe Gln Ser Ser Ser Arg Ser Ser
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Tyr Tyr Gly Pro Trp Gly Arg Ser Ala Ala Trp Ala Ser Arg Arg Ser
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Ser Trp Asn Ser Leu Lys His Lys Pro Pro Ser Ala Glu His Glu Ser
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Leu Leu Ser Ala Glu Arg Gly Gly Gly Ala Arg Val Cys Glu Val Ala

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Ala Asp Glu Gly Pro Pro Arg Ala Ala Pro Leu His Thr Pro His Ala
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His His Val His His Gly Pro His Leu Ala His Arg His Arg His His
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Arg Arg Thr Leu Ser Leu Asp Asn Arg Asp Ser Val Asp Leu Ala Glu
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Leu Val Pro Ala Val Gly Ala His Pro Arg Ala Ala Trp Arg Ala Ala
1380 1385 1390

Gly Pro Ala Pro Gly His Glu Asp Cys Asn Gly Arg Met Pro Ser Ile
1395 1400 1405

Ala Lys Asp Val Phe Thr Lys Met Gly Asp Arg Gly Asp Arg Gly Glu
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Asp Glu Glu Glu Ile Asp Tyr Val Ser Gly Gly Gly Ala Glu Gly Asp
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Leu Thr Leu Cys Phe Arg Val Arg Lys Met Ile Asp Val Tyr Lys Pro
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Asp Trp Cys Glu Val Arg Glu Asp Trp Ser Val Tyr Leu Phe Ser Pro
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Glu Asn Arg Leu Arg Asp Leu Gly Trp Val Ser Leu Glu Cys Gln Gly
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Lys Val Gly Asp Leu Val Val Trp Val Tyr Gly Gln Arg Arg Gln Arg
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Gln Thr Ile Ile Ala His Lys Leu Phe Asp Tyr Val Val Leu Ala Phe
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Ile Phe Leu Asn Cys Ile Thr Ile Ala Leu Glu Arg Pro Gln Ile Glu
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Ala Gly Ser Thr Glu Arg Ile Phe Leu Thr Val Ser Asn Tyr Ile Phe
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Thr Ala Ile Phe Val Gly Glu Met Thr Leu Lys Val Val Ser Leu Gly
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Leu Tyr Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu

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Asp Gly Phe Leu Val Phe Val Ser Ile Ile Asp Ile Val Val Ser Leu
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Ala Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg Val Leu Arg
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Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Pro Gly
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Leu Lys Leu Val Val Glu Thr Leu Ile Ser Ser Leu Lys Pro Ile Gly
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Asn Ile Val Leu Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu
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Gly Val Gln Leu Phe Lys Gly Lys Phe Tyr His Cys Leu Gly Val Asp
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Thr Arg Asn Ile Thr Asn Arg Ser Asp Cys Met Ala Ala Asn Tyr Arg
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Trp Val His His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met
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Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asn Ile Met Tyr
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Asn Gly Leu Asp Ala Val Ala Val Asp Gln Gln Pro Val Thr Asn His
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Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ser
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Phe Phe Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His
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Lys Cys Arg Gln His Gln Glu Ala Glu Glu Ala Arg Arg Arg Glu Glu
1780 1785 1790

Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Lys Ala Gln Arg Leu
1795 1800 1805

Pro Tyr Tyr Ala Thr Tyr Cys His Thr Arg Leu Leu Ile His Ser Met
1810 1815 1820

Cys Thr Ser His Tyr Leu Asp Ile Phe Ile Thr Phe Ile Ile Cys Leu

1825 1830 1835 1840

Asn Val Val Thr Met Ser Leu Glu His Tyr Asn Gln Pro Thr
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<213> HUMAN

<220>
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20 25 30

Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg Cys Phe Leu Glu
35 40 45

Glu Asn Phe Thr Ile Gln Gly Asp Val Ala Leu Pro Pro Tyr Tyr Gln
50 55 60

Pro Glu Glu Asp Asp Glu Met Pro Phe Ile Cys Ser Leu Ser Gly Asp

65 70 75 80

Asn Gly Ile Met Gly Cys His Glu Ile Pro Pro Leu Lys Glu Gln Gly
85 90 95

Arg Glu Cys Cys Leu Ser Lys Asp Asp Val Tyr Asp Phe Gly Ala Gly
100 105 110

Arg Gln Asp Leu Asn Ala Ser Gly Leu Cys Val Asn Trp Asn Arg Tyr
115 120 125

Tyr Asn Val Cys Arg Thr Gly Ser Ala Asn Pro His Lys Gly Ala Ile
130 135 140

Ser Phe Asp Asn Ile Gly Tyr Ala Trp Ile Val Ile Phe Gln Val Ile
145 150 155 160

Thr Leu Glu Gly Trp Val Ala Ile Met Tyr Tyr Val Met Asp Ala Leu
165 170 175

Ser Phe Tyr Asn Phe Val Tyr Phe Ile Leu Leu Ile Ile
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<213> rat

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<212> PRT
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<220>
<223> rat alpha-I partial sequence

<400> 22

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            20                  25                  30

Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg Cys Phe Leu Glu
        35                  40                  45

Glu Asn Phe Thr Ile Gln Gly Asp Val Ala Leu Pro Pro Tyr Tyr Gln
    50                  55                  60

Pro Glu Glu Asp Asp Glu Met Pro Phe Ile Cys Ser Leu Thr Gly Asp
65                  70                  75                  80

Asn Gly Ile Met Gly Cys His Glu Ile Pro Pro Leu Lys Glu Gln Gly
                85                  90                  95

Arg Glu Cys Cys Leu Ser Lys Asp Asp Val Tyr Asp Phe Gly Ala Gly
            100                 105                 110

Arg Gln Asp Leu Asn Ala Ser Gly Leu Cys Val Asn Trp Asn Arg Tyr
        115                 120                 125

Tyr Asn Val Cys Arg Thr Gly Asn Ala Asn Pro His Lys Gly Ala Ile
    130                 135                 140

Asn Phe Asp Asn Ile Gly Tyr Ala Trp Ile Val Ile Phe Gln Val Ile
145                 150                 155                 160

Thr Leu Glu Gly Trp Val Glu Ile Met Tyr Tyr Val Met Asp Ala His
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Ser Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile
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Gly Ala Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala
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Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu
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Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn
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Ala Val Glu Met Val Val Lys Met Val Ala Leu Gly Ile Phe Gly Lys
165 170 175

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Leu Ala Pro Glu Ser Pro Gly Thr Glu Cys Gly Ala Asp Leu Gly Ala
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Asp Glu Glu Gln Pro Val Pro Tyr Pro Ala Leu Ala Ala Thr Val Phe
65                  70                  75                  80

Phe Cys Leu Gly Gln Thr Thr Arg Pro Arg Ser Trp Cys Leu Arg Leu
                85                  90                  95

Val Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu
            100                 105                 110

Asn Cys Val Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Val Glu Cys
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Arg Ser Glu Arg Cys Ser Ile Leu Glu Ala Phe Asp Asp Phe Ile Phe
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Ala Phe Phe Ala Val Glu Met Val Ile Lys Met Val Ala Leu Gly Leu
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Phe Gly Gln Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe
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Phe Ile Val Met Ala Gly Met Met Glu Tyr Ser Leu Asp Gly His Lys
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Val Ser Leu Ser Ala Ile Arg Thr Val Arg Val Leu Arg Pro Leu Arg
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Asp Thr Leu Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val
225                 230                 235                 240

Phe Phe Ile Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu
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Arg Asn Arg Cys Phe Leu Asp Ser Ala Phe Val Arg Asn Asn Asn Leu
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Ile Pro Ser Arg Arg Glu Leu Arg Val Gln Cys Thr Leu Gly Trp Glu
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Ala Tyr Gly Gln Pro Gln Ala Glu Asp Gly Gly Ala Gly Arg Asn Ala
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Cys Ile Asn Trp Asn Gln Tyr Tyr Asn Val Cys Arg Ser Gly Glu Phe
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Asn Pro His Asn Gly Ala Ile Asn Phe Asp Asn Ile Gly Tyr Ala Trp
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Ile Ala Ile Phe Gln Val Ile Thr Leu Glu Gly Trp Val Asp Ile Met
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Tyr Tyr Val Met Asp Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe Ile
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Val Ile Ala Thr Gln Phe Ser Glu Thr Lys Gln Arg Glu Asn Gln Leu
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Met Arg Glu Gln Arg Ala Arg Tyr Leu Ser Asn Asp Ser Thr Leu Ala
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His Gly Gln Gly Pro Gly Arg Arg Pro Arg Arg Ala Gly Arg Arg Thr
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Ala Ser Val His His Leu Val Tyr His His His His His His His His
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Pro Ser Pro Gly His Gly Pro Pro Asp Ser Glu Ser Val His Ser Ile
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Tyr His Ala Asp Cys His Val Glu Gly Pro Gln Glu Arg Ala Arg Val
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Ala His Ser Ile Ala Thr Ala Ala Ser Leu Lys Leu Ala Ser Gly Leu
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Gly Thr Met Asn Tyr Pro Thr Ile Leu Pro Ser Gly Thr Val Asn Ser
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Lys Gly Gly Thr Ser Ser Arg Pro Lys Gly Leu Arg Gly Ala Gly Ala
625                 630                 635                 640

Pro Gly Ala Ala Val His Ser Pro Leu Ser Leu Gly Ser Pro Arg Pro
                645                 650                 655

Tyr Glu Lys Ile Gln Asp Val Val Gly Glu Gln Gly Leu Gly Arg Ala
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Ser Ser His Leu Ser Gly Leu Ser Val Pro Cys Pro Leu Pro Ser Pro
        675                 680                 685

Gln Ala Gly Thr Leu Thr Cys Glu Leu Lys Ser Cys Pro Tyr Cys Ala
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Ser Ala Leu Glu Asp Pro Glu Phe Glu Phe Ser Gly Ser Glu Ser Gly
705                 710                 715                 720

Asp Ser Asp Ala His Gly Val Tyr Glu Phe Thr Gln Asp Val Arg His
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Gly Asp Cys Arg Asp Pro Val Gln Gln Pro His Glu Val Gly Thr Pro
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Gly His Ser Asn Glu Arg Arg Arg Thr Pro Leu Arg Lys Ala Ser Gln
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Pro Gly Gly Ile Gly His Leu Trp Ala Ser Phe Ser Gly Lys Leu Arg
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Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr Ser Met
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Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Ala Cys Gly Pro Leu Gly
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Tyr Ile Arg Asn Pro Tyr Asn Ile Phe Asp Gly Ile Val Val Val Ile
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Ser Val Trp Glu Ile Val Gly Gln Ala Asp Gly Gly Gln Ser Val Leu
865                 870                 875                 880

Arg Thr Phe Arg Leu Leu Arg Val Leu Lys Leu Val Arg Phe Leu Pro
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Ala Leu Arg Arg Gln Leu Val Val Leu Met Arg Thr Met Asp Asn Val
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Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe Ser Ile
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Leu Gly Met His Leu Phe Gly Cys Lys Phe Ser Leu Lys Thr Asp Ser
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Gly Asp Thr Val Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp Ala
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Ile Val Thr Val Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn Val Val
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Leu Tyr Asn Gly Met Ala Ser Thr Ser Ser Trp Ala Ala Leu Tyr Phe
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Ala Thr Phe Thr Asn Phe Gly Met Ala Phe Leu Thr Leu Phe Arg Val
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Ser Thr Gly Asp Asn Trp Asn Gly Ile Met Lys Asp Thr Leu Arg Glu
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Cys Thr Arg Glu Asp Lys His Cys Leu Ser Tyr Leu Pro Ala Leu Ser
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Pro Val Tyr Phe Val Thr Phe Met Leu Val Ala Gln Phe Val Leu Val
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Asn Val Val Val Ala Val Leu Met Lys His Leu Glu Glu Ser Asn Lys
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Gly Thr Gln Pro Asp Thr Pro Asn Leu Leu Val Val Arg Lys Val Ser
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Val Ser Arg Met Leu Ser Leu Pro Asn Asp Ser Tyr Met Phe Arg Pro
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Ser Leu Ser Leu Ser Arg Ile Leu Cys Arg Gln Glu Ala Met His Ser
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35 40 45

His Pro Asp Leu Ala Pro Val Ala Phe Phe Cys Leu Arg Gln Thr Thr
50 55 60

Ser Pro Arg Asn Trp Cys Ile Lys Met Val Cys Asn Pro Trp Phe Glu
65 70 75 80

Cys Val Ser Met Leu Val Ile Leu Leu Asn Cys Val Thr Leu Gly Met
85 90 95

Tyr Gln Pro Cys Asp Asp Met Glu Cys Leu Ser Asp Arg Cys Lys Ile
100 105 110

Leu Gln Val Phe Asp Asp Phe Ile Phe Ile Phe Phe Ala Met Glu Met
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Val Leu Lys Met Val Ala Leu Gly Ile Phe Gly Lys Lys Cys Tyr Leu

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Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val Met Ala Gly Met
145 150 155 160

Val Glu Tyr Ser Leu Asp Leu Gln Asn Ile Asn Leu Ser Ala Ile Arg
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Thr Val Arg Val Leu Arg Pro Leu Lys Ala Ile Asn Arg Val Pro Ser
180 185 190

Leu Arg Ile Leu Val Asn Leu Leu Leu Asp Thr Leu Pro Met Leu Gly
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Glu Asn Phe Thr Ile Gln Gly Asp Val Ala Leu Pro Pro Tyr Tyr Gln
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Pro Glu Glu Asp Asp Glu Met Pro Phe Ile Cys Ser Leu Thr Gly Asp
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Asn Gly Ile Met Gly Cys His Glu Ile Pro Pro Leu Lys Glu Gln Gly
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Arg Glu Val Cys Leu Ser Lys Asp Asp Val Tyr Asp Phe Gly Ala Gly
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Arg Gln Asp Leu Asn Ala Ser Gly Leu Cys Val Asn Trp Asn Arg Tyr
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Tyr Asn Val Cys Arg Thr Gly Asn Ala Asn Pro His Lys Gly Ala Ile
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Thr Leu Glu Gly Trp Val Glu Ile Met Tyr Tyr Val Met Asp Ala His
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Ile Asn Leu Cys Leu Val Leu Ile Ala Thr Gln Phe Ser Glu Thr Lys

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Gln Arg Asn His Arg Leu Met Leu Glu Gln Arg Gln Arg Tyr Leu Ser
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Ser Asp Leu Gly Lys Glu Glu Glu Gln Glu Asp Gly Ala Ala Arg Leu
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Thr Val Ser Met Gly Ile Glu His His Glu Gln Pro Glu Glu Leu Thr
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Glu Met Ile Leu Lys Leu Ala Ala Phe Gly Leu Phe Asp Tyr Leu Arg

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Asn Pro Tyr Asn Ile Phe Asp Ser Ile Ile Val Ile Ile Ser Ile Trp
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Glu Ile Val Gly Gln Ala Asp Ser Gly Leu Ser Val Leu Arg Thr Ser
675 680 685

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Met Leu Leu Met Leu Phe Ile Phe Ile Phe Ser Ile Leu Gly Ile Asp
725 730 735

Ile Phe Gly Cys Lys Phe Ser Leu Arg Thr Asp Thr Gly Asp Thr Val
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Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp Ala Ile Val Thr Val
755 760 765

Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn Val Val Leu Tyr Asn Gly
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Met Ala Ser Thr Thr Pro Trp Ala Ser Leu Tyr Phe Val Ala Leu Met
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Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu Val Ala Ile Leu Val
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Glu Gly Phe Gln Ala Glu Gly Asp Ala Asn Arg Ser Tyr Ser Asp Glu
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Asp Gln Ser Ser Ser Asn Leu Glu Glu Leu Asp Lys Leu Pro Glu Gly
835 840 845

Leu Asp Asn Arg Arg Asp Leu Lys Leu Cys Pro Ile Pro Met Thr Pro
850 855 860

Asn Gly His Leu Asp Pro Ser Leu Pro Leu Gly Ala His Leu Gly Pro
865 870 875 880

Ala Gly Thr Met Gly Thr Ala Pro Arg Leu Ser Leu Gln Pro Asp Pro
885 890 895

Val Leu Val Ala Arg Asp Ser Arg Lys Ser Ser Tyr Trp Ser Leu Gly

900 905 910

Arg Met Ser Tyr Asp Gln Arg Ser Leu Ser Ser Ser Arg Ser Ser Tyr
915 920 925

Tyr Gly Pro Gly Gly Arg Ser Gly Thr Trp Ala Ser Arg Arg Ser Ser
930 935 940

Trp Asn Ser Leu Lys His Lys Pro Pro Ser Ala Glu His Glu Ser Leu
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Leu Ser Gly Glu Gly Gly Gly Ser Cys Val Arg Ala Cys Glu Gly Ala
965 970 975

Arg Glu Glu Ala Pro Thr Arg Thr Ala Pro Leu His Ala Pro His Arg
980 985 990

His His Ala His His Gly Pro His Leu Ala His Arg His Arg His His
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Asp Glu Glu Glu Ile Asp Tyr Thr Leu Cys Phe Arg Val Arg Lys Met
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Ile Cys Cys Val Tyr Lys Pro Asp Trp Cys Glu Val Arg Glu Asp Trp
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Ser Val Tyr Leu Phe Ser Pro Glu Asn Lys Phe Arg Ile Leu Cys Gln
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Thr Ile Ile Ala His Lys Leu Phe Asp Tyr Val Val Leu Ala Phe Ile
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Phe Leu Asn Cys Ile Thr Ile Ala Leu Glu Arg Pro Gln Ile Glu Ala
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Val Glu Thr Leu Ile Ser Ser Leu Lys Pro Ile Gly Asn Ile Val Leu
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Phe Lys Gly Lys Phe Tyr His Cys Leu Gly Val Asp Thr Arg Asn Ile
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Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met Ser Leu Phe Val
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Leu Pro Gln Val Gly Asn Leu Gly Leu Leu Phe Met Leu Leu Phe Phe
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Arg Thr Cys Leu Ser Ser Leu Gln Phe Val Ser Pro Leu Tyr Phe Val
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Ser Phe Val Leu Thr Ala Gln Phe Val Leu Ile Asn Val Val Val Ala

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Val Leu Met Lys His Leu Asp Asp Ser Asn Lys Glu Ala Gln Glu Asp
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Ala Glu Met Asp Ala Glu Ile Glu Leu Glu Met Ala His Gly Ser Gly
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Pro Cys Pro Gly Pro Cys Pro Gly Pro Cys Pro Cys Pro Cys Pro Cys
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Pro Cys Ser Gly Pro Arg Cys Pro Leu Val Thr Trp Gly Ser Gly Ala
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Met Asp Arg Glu Gly Gln Val Leu Glu Ala His Arg Glu Ser Pro Val
1745 1750 1755 1760

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Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn
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Pro Trp Phe Glu Arg Ile Ser Met Leu Val Ile Leu Leu Asn Cys Val
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Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln
            100                 105                 110

Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe
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Ala Val Glu Met Val Val Lys Met Val Ala Leu Gly Ile Phe Gly Lys
    130                 135                 140

Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val
145                 150                 155                 160

Ile Ala Gly Met Leu Glu Tyr Ser Leu Asp Leu Gln Asn Val Ser Phe
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Ser Ala Val Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn
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Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp Thr Leu
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Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile
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Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg
225                 230                 235                 240

Cys Phe Leu Pro Glu Asn Phe Ser Leu Pro Leu Ser Val Asp Leu Glu
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Arg Tyr Tyr Gln Thr Glu Asn Glu Asp Glu Ser Pro Phe Ile Cys Ser
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Tyr Asn Ser Ser Ser Asn Thr Thr Cys Val Asn Trp Asn Gln Tyr Tyr
305 310 315 320

Thr Asn Cys Ser Ala Gly Glu His Asn Pro Phe Lys Gly Ala Ile Asn
325 330 335

Phe Asp Asn Ile Gly Tyr Ala Trp Ile Ala Ile Phe Gln Val Ile Thr
340 345 350

Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser
355 360 365

Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe
370 375 380

Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu
385 390 395 400

Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe
405 410 415

Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys
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Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala
435 440 445

Arg Arg Leu Ala Gln Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu
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Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Glu Thr Gln Pro Ser Ser
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Ser Cys Ser Arg Ser His Arg Arg Leu Ser Val His His Leu Val His
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His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu
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Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Ser Pro
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Val His Thr Ser Pro Pro Pro Glu Thr Leu Lys Glu Lys Ala Leu Val
595 600 605

Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr Ser Leu Asn Ile
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Ser Pro Ser Glu Ser Pro Ala Ala Glu Arg Gly Ala Glu Leu Gly Ala
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Asp Glu Glu Gln Arg Val Pro Tyr Pro Ala Leu Ala Ala Thr Val Phe
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Phe Cys Leu Gly Gln Thr Thr Arg Pro Arg Ser Trp Cys Leu Arg Leu
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Val Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu
100 105 110

Asn Cys Val Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Val Glu Cys
115 120 125

Gly Ser Glu Arg Cys Asn Ile Leu Glu Ala Phe Asp Ala Phe Ile Phe
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Ala Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu
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Asp Thr Leu Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val
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Phe Phe Ile Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu
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Arg Asn Arg Cys Phe Leu Asp Ser Ala Phe Val Arg Asn Asn Asn Leu
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Thr Phe Leu Arg Pro Tyr Tyr Gln Thr Glu Glu Gly Glu Glu Asn Pro
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    290                 295                 300

Ile Pro Gly Arg Arg Glu Leu Arg Met Pro Cys Thr Leu Gly Trp Glu
305                 310                 315                 320

Ala Tyr Thr Gln Pro Gln Ala Glu Gly Val Gly Ala Ala Arg Asn Ala
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Cys Ile Asn Trp Asn Gln Tyr Tyr Asn Val Cys Arg Ser Gly Asp Ser
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Tyr Tyr Val Met Asp Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe Ile
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Val Ile Ala Thr Gln Phe Ser Glu Thr Lys Gln Arg Glu Ser Gln Leu
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Arg Trp Gln Ser Arg Trp Arg Lys Lys Val Asp Pro Ser Ala Val Gln
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Val Cys Glu Val Ala Ala Asp Glu Gly Pro Pro Arg Ala Ala Pro Leu
 65                  70                  75                  80

His Thr Pro His Ala His His Ile His His Gly Pro His Leu Ala His
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Arg His Arg His His Arg Arg Thr Leu Ser Leu Asp Asn Arg Asp Ser
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Val Asp Leu Ala Glu Leu Val Pro Ala Val Gly Ala His Pro Arg Ala
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Gly Asp Arg Gly Glu Asp Glu Glu Glu Ile Asp Tyr Thr Leu Cys Phe
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Arg Val Arg Lys Met Ile Asp Val Tyr Lys Pro Asp Trp Cys Glu Val
            180                 185                 190

Arg Glu Asp Trp Ser Val Tyr Leu Phe Ser Pro Glu Asn Arg Phe Arg
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Val Leu Cys Gln Thr Ile Ile Ala His Lys Leu Phe Asp Tyr Val Val
    210                 215                 220

Leu Ala Phe Ile Phe Leu Asn Cys Ile Thr Ile Ala Leu Glu Arg Pro
225                 230                 235                 240
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Gln Ile Glu Ala Gly Ser Thr Glu Arg Ile Phe Leu Thr Val Ser Asn
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Tyr Ile Phe Thr Ala Ile Phe Val Gly Glu Met Thr Leu Lys Val Val
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Ser Leu Gly Leu Tyr Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp
        275                 280                 285

Asn Val Leu Asp Gly Phe Leu Val Phe Val Ser Ile Ile Asp Ile Val
    290                 295                 300

Val Ser Leu Ala Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg
305                 310                 315                 320

Val Leu Arg Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg
                325                 330                 335

Ala Pro Gly Leu Lys Leu Val Val Glu Thr Leu Ile Ser Ser Leu Lys
            340                 345                 350

Pro Ile Gly Asn Ile Val Leu
        355
```

OPPEDAHL & LARSON

FILE NO. NMED.P-001-2

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My citizenship, residence and post office address are as listed below next to my name.

I believe I am the original, first and [ ] sole/[x]joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: Novel Human Calcium Channels and Related Probes, Cell Lines and Methods
the specification of which

(a) [X] is attached hereto.

(b) [ ] was filed on _____ as Application Serial No. _____ and was amended on _____.

(c) [ ] was described and claimed in International Application No. _____ filed on _____ and amended on _____.

Acknowledgment of Duty of Disclosure

I hereby state that I have reviewed and understood the content of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the patentability of the subject matter claimed in this application in accordance with Title 37, Code of Federal Regulations § 1.56(a).

Continuation-In-Part Application

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status)(patented,pending,abandoned)
09/030,482	February 25, 1999	pending

Power of Attorney

I hereby appoint Carl Oppedahl, PTO Reg. NO. 32,746 and Marrina T. Larson, PTO Reg. No. 32,038 of the firm of OPPEDAHL & LARSON LLP, whose address is PO Box 5270, 611 main Street, Frisco, CO 80443-5270 as attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

SEND CORRESPONDENCE TO:	DIRECT TELEPHONE CALLS TO:
OPPEDAHL & LARSON LLP PO BOX 5270 FRISCO, CO 80443-5270	OPPEDAHL & LARSON (970) 668-2050

OPPEDAHL & LARSON

FILE NO. NMED.P-001-2

Claim for Priority

I hereby claim priority under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have identified any foreign applications for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

EARLIEST FOREIGN APPLICATION(S), FILED WITHIN TWELVE MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION			
COUNTRY APPLICATION NO.	DATE OF FILING (day/month/year)	DATE OF ISSUE (day/month/year)	PRIORITY CLAIMED
			YES[ ] NO[ ]
			YES[ ] NO[ ]
			YES[ ] NO[ ]

FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION			
COUNTRY APPLICATION NO.	DATE OF FILING (day/month/year)	DATE OF ISSUE (day/month/year)	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR	LAST NAME **SNUTCH**	FIRST NAME **TERRY**	MIDDLE NAME **P.**
RESIDENCE & CITIZENSHIP	CITY OF RESIDENCE **VANCOUVER**	STATE OR COUNTRY OF RESIDENCE **CANADA**	COUNTRY OF CITIZENSHIP **CANADA**
POST OFFICE ADDRESS **3963 W. 24TH Avenue**		CITY **VANCOUVER**	STATE/COUNTRY ZIP CODE **CANADA V6S 1M1**
DATE July 1, 1999		SIGNATURE	

[X] Signature for additional joint inventor attached. Number of Pages 1.
[ ] Signature by Administrator(trix) or legal representative for deceased or incapacitated inventor. Number of Pages ___.
[ ] Signature for inventor who refuses to sign or cannot be reached by person authorized under 37 CFR § 1.47. Number of Pages ___.

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FILE NO. NMED.P-001-2

NAME OF SECOND INVENTOR	LAST NAME **BAILLIE**	FIRST NAME **DAVID**	MIDDLE NAME **L.**
RESIDENCE & CITIZENSHIP	CITY OF RESIDENCE **VANCOUVER**	STATE OR COUNTRY OF RESIDENCE **CANADA**	COUNTRY OF CITIZENSHIP **CANADA**
POST OFFICE ADDRESS **29 North Kootenay Street**		CITY **VANCOUVER**	STATE/COUNTRY ZIP CODE **CANADA V5K 3P7**
DATE July 1, 1999		SIGNATURE David L Baillie	

NAME OF THIRD INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
RESIDENCE & CITIZENSHIP	CITY OF RESIDENCE	STATE OR COUNTRY OF RESIDENCE	COUNTRY OF CITIZENSHIP
POST OFFICE ADDRESS		CITY	STATE/COUNTRY ZIP CODE
DATE		SIGNATURE	

NAME OF FOURTH INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
RESIDENCE & CITIZENSHIP	CITY OF RESIDENCE	STATE OR COUNTRY OF RESIDENCE	COUNTRY OF CITIZENSHIP
POST OFFICE ADDRESS		CITY	STATE/COUNTRY ZIP CODE
DATE		SIGNATURE	

NAME OF FIFTH INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
RESIDENCE & CITIZENSHIP	CITY OF RESIDENCE	STATE OR COUNTRY OF RESIDENCE	COUNTRY OF CITIZENSHIP
POST OFFICE ADDRESS		CITY	STATE/COUNTRY ZIP CODE
DATE		SIGNATURE	